

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 January 2003 (23.01.2003)

PCT

(10) International Publication Number
WO 03/005995 A1

(51) International Patent Classification⁷: **A61K 9/32**, 9/34, 9/36, 9/38, 9/40, 9/58, 9/60, 9/62, 9/64

(21) International Application Number: PCT/US01/21615

(22) International Filing Date: 10 July 2001 (10.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant: **AEROPHARM TECHNOLOGY INCORPORATED** [US/US]; 18 Mayfield Avenue, Campus Plaza 9 - Raritan Center, Edison, NJ 08837 (US).

(72) Inventors: **ADJEL, Akwete, L.**; 15 Tillman Court, Bridgewater, NJ 08807 (US). **ZHU, Yaping**; 284 South 10th Street, Apt. A, Highland Park, NJ 08904 (US). **CUTIE, Anthony, J.**; 10 Tillman Court, Bridgewater, NJ 08807 (US).

(74) Agents: **ROSENSTOCK, Jerome** et al.; Frommer Lawrence & Haug LLP, 745 Fifth Avenue, New York, NY 10151 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/005995 A1

(54) Title: CORE FORMULATION COMPRISING PIOGLITAZONE HYDROCHLORIDE AND A BIGUANIDE

(57) Abstract: This invention relates to a modulating formulation comprising pioglitazone hydrochloride and a biguanide, e.g. metformin. In particular, the product comprises a core of the biguanide, e.g. metformin, at least a portion thereof has a layer or coat thereon of pioglitazone.

Core Formulation Comprising Pioglitazone Hydrochloride and a Biguanide

This application claims priority from U.S. provisional application Serial No. 60/201,057, filed May 1, 2000, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

5 **Field of the Invention**

This invention relates to a core formulation, and, more particularly, to a core formulation comprising a first layer comprising pioglitazone, which covers at least a portion of a core comprising a biguanide, metformin (i.e., glucophage), with a modulating release polymer comprising a silicate.

10 **Description of the Related Art**

Metformin and pioglitazone, or their salts such as the hydrochlorides, maleates, tartrates, etc., are two active ingredients of anti-diabetic drugs that are used to treat diabetic patients, e.g. human beings. These two active agents are administered orally to patients in need thereof in protocols calling for the single
15 administration of either ingredient. Heretofore, there has not been revealed or hinted at combining both ingredients and certainly not a physically combined core formulation comprising both ingredients. The use of such a core formulation is advantageous to patients and prescribers because both medicaments are synergistic to each other in the body when used in the management of blood glucose control,
20 i.e., diabetes. Furthermore, the use of a modulating agent, like silica gel, in the preparation, controls the rate of drug release over a clinically meaningful period to enable better control of the effect of the medicinal agents in such preparation.

SUMMARY OF THE INVENTION

This invention relates to a core formulation, and, more particularly, to
25 a core formulation comprising a first layer comprising pioglitazone hydrochloride, which covers at least a portion of a core comprising a biguanide, e.g. metformin, one or both of which are intimately dispersed in a silicate based modulating agent.

DETAILED DESCRIPTION OF THE INVENTION

A typical biguanide is metformin. It typically is used clinically as a
30 pharmaceutically acceptable salt, preferably the hydrochloride salt. A commercial form of metformin hydrochloride is available as glucophage. Its chemical name is N,N-dimethylimidodicarbonimidic diamide hydrochloride. Metformin

hydrochloride is a hydrochloride salt of metformin base, and as used herein, "metformin" means the base compound as well as its pharmaceutically acceptable salts. Metformin is used clinically to manage non-insulin dependent diabetes mellitus or "NIDDM", particularly in patients who are not effectively treated with a sulfonylurea. While it is not chemically related to the sulfonylureas, it is routinely utilized in combination with a sulfonylurea, and has been shown to be synergistic in some cases. Other biguanides such as phenformin, buformin etc. can also be used. Additionally, in the treatment of a diabetic patient the metformin, for example, and the pioglitazone hydrochloride are present in effective amounts to provide such treatment.

Metformin is an active ingredient for a commercially available drug employed to treat diabetes mellitus in a host or mammal, e.g. a human being, another animal. The typical daily effective dose for the oral treatment of a mammal, i.e., a human, ranges from about 500 mg to about 2550 mg. Typically, the dose is a single dose of about 500 mg to about 850 mg.

Pioglitazone hydrochloride, (ACTOS®), is an active ingredient for a commercially available drug employed to treat diabetes mellitus in a host, e.g. a human being. The typical daily effective dose for the oral administration to a mammal, e.g. a human being, ranges from about 15 mg to about 45 mg, given as a single dose.

Silicates are pharmaceutical excipients generally regarded as safe and used therefore to prepare a variety of pharmaceutical systems well documented in the patent literature. In this regard, reference is made to *Remington's Pharmaceutical Sciences, 18th Edition, Inorganic Pharmaceutical Chemistry, Silicon, pp 340-341, 1990.*

Heretofore, the silicates have not been shown to modulate the release of the hypoglycemic drugs metformin and pioglitazone hydrochloride when administered together to try to improve the control and effectiveness of either drug, although co-administration of the two has been proposed [*Whitcomb; et al., United States Patent No. 6,011,049*]. However, a combined form of the drugs, i.e. a single integral unit thereof has not heretofore been reported. The present invention provides such a single integral unit in the form of a core formulation.

A typical silicate for this purpose is Purified Siliceous Earth (National Formulary XVI), also known in some forms as silica gel or fumed silica. It is typically used in oral pharmaceutical preparations as a bulking agent. As used herein, "silicate" means silicic acid, disilicic acid, trisilic acid, metasilicic acid, and orthosilicic acid in their free or salt forms; silicon dioxide in either of its amorphous, crystalline, or precipitated forms; diatomaceous earth; Fuller's earth, Kieselhurh, Celite; talc; attapulgate; micas; clays such as montmorillonite (Montmorillonite™), kaolin, aluminum oxide (Hydrargilite), bentone (Bentonite™), bentonite (Bentonite Magma™) and pumice; silanes and siloxanes. These are used typically as adsorbents, carriers, dispersants, fillers, thickeners.

As indicated above, the relative concentrations of each drug is such that a first layer comprising pioglitazone hydrochloride is prepared. The first layer covers at least a portion of a core comprising metformin with a portion or all of the amount of the silicate. Depending upon the rate of administration of the core preparation, the metabolism of the patient destined to be treated, and the desired concentrations of each ingredient for each drug, the first layer may cover only a portion of the core or encompass the entire core. For example, one quarter of the core to about three fourths of the tablet core. The first layer should comprise pioglitazone hydrochloride with or without any silicate, because its dose requirement is lower compared to metformin. Additionally, pioglitazone hydrochloride is slightly non-polar, its solubility rate is slower, and its absorption rate thus is dependent on its dissolution rate in the contents of the gastrointestinal tract compared with metformin.

It is to be understood, depending upon the desired rate of administration to the patient, either the first layer or the core may additionally contain a mixture of the two active ingredients or both the first layer and the core may contain the two active ingredients with different and varying concentrations of one or both active ingredients.

The first layer of the core comprises pioglitazone hydrochloride in an amount of about 0.01 % to about 20% of the total weight of the core formulation, whereas, the metformin in the core is present in an amount of about 10% to about 97.5% of the total weight of the core formulation.

Where combinations of the two active ingredients are present in the first layer and/or the core, the amounts of pioglitazone hydrochloride range from about 1 mg to about 45 mg whereas the metformin ranges from about 100 mg to about 2550 mg.

- 5 Finally, it is to be understood that a third pharmacologically active material, e.g. a drug, such as for example a sulfonylurea, an α -glucosidase inhibitor, a meglitinide, and an ACE inhibitor may be employed in an admixture with the active ingredients in the first layer and/or the core.

- The α -glucosidase inhibitors [Jean-Bernard Ducep et al., US
 10 Patent No. 5,504,078], bisglucosylmoranoline derivatives [UK Patent No. GB 2 088 365 A], and glucosylmoranoline derivatives [European Patent No. 87112480.6] include the following medicaments: 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[6,7-dideoxy-7-D-glucoheptopyranosyl]imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(1-deoxy-D-fructofuranosyl)imino]-D-glucitol;
 15 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[6-deoxy-1-(6-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[6,7-dideoxy-1-(6-O-D-glucopyranosyl)-7-.alpha.-D-glucoheptopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)methylimino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(4-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-{[2(1-D-arabinofuranose)ethyl]imino}-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(6-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-{[4-deoxy-1-(4-O-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl]methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-{[4-deoxy-1-(6-O-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl]methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(6-deoxy-1-O-methyl-6- β -D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(6,7-dideoxy-1-O-methyl-7- β -D-glucoheptopyranosyl)imino]-D-glucitol; 1.5-

Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(1-deoxy-2-O-methyl-β-D-fructofuranosyl)imino]-D-glucitol, 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-1-O-methyl-4-β-D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[6-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-.alpha.-D -glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[6,7-dideoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-7-.alpha.-D-glucoheptopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-1-O-methyl-4-β-D-glucopyranosyl)methylimino]-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(1-O-methyl-4-O-8-D-glucopyranosyl)-.alpha.-D -glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-1,5-{[2-(1-O-methyl-1-β-D-arabinofuranosyl)ethyl]imino}-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-{[4-deoxy-1-(1-O-methyl-4-O-β-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl]methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-4-O(.alpha.,D-glucopyranosyl)-N-{[4-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-4-.alpha.-D-glucopyranosyl]methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[6,7-dideoxy-7-D-glucoheptopyranosyl]imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(1-deoxy-D-fructofuranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[6-deoxy-1-(6-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[6,7-dideoxy-1-(6-O-D-glucopyranosyl)-7-.alpha.-D -glucoheptopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(4-deoxy-4-D-glucopyranosyl)methylimino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(4-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-{[2(1-D-arabinofuranose)ethyl]imino}-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(6-O-D-glucopyranosyl)-.alpha.-D-glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-{[4-deoxy-1-

(4-O-D-glucopyranosyl)-4-.alpha.-D -glucopyranosyl)methyl}-1,5-imino-D-glucitol;
 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-{[4-deoxy-1-(6-O-D-
 glucopyranosyl)-4-.alpha.-D -glucopyranosyl)methyl}-1,5-imino-D-glucitol; 1.5-
 Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(6-deoxy-1-O-methyl-6-β-D-
 5 glucopyranosyl)-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-
 [(6,7-dideoxy-1-O-methyl-7-β-D-glucoheptopyranosyl) imino]-D-glucitol; 1.5-
 Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[(1-deoxy-2-O-methyl-β-D-
 fructofuranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-
 [(4-deoxy-1-O-methyl-4-β-D-glucopyranosyl)imino]-D-glucitol; 1.5-Dideoxy-6-
 10 O(.alpha.,D-glucopyranosyl)-N-[6-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-
 .alpha.-D -glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-
 glucopyranosyl)-N-[6,7-dideoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-7-
 .alpha.-D-glucoheptopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-
 glucopyranosyl)-1,5-[(4-deoxy-1-O-methyl-4-β-D-glucopyranosyl)methylimino]-D-
 15 glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-N-[4-deoxy-1-(1-O-methyl-4-
 O-β-D-glucopyranosyl)-.alpha.-D -glucopyranosyl]-1,5-imino-D-glucitol; 1.5-
 Dideoxy-6-O(.alpha.,D-glucopyranosyl)-1,5-[[2-(1-O-methyl-1-β-D-
 arabinofuranosyl)ethyl]imino]-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-
 glucopyranosyl)-N-[4-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-.alpha.-D -
 20 glucopyranosyl]-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-glucopyranosyl)-
 N-([4-deoxy-1-(1-O-methyl-4-O-β-D-glucopyranosyl)-4-.alpha.-D-
 glucopyranosyl)methyl}-1,5-imino-D-glucitol; 1.5-Dideoxy-6-O(.alpha.,D-
 glucopyranosyl)-N-([4-deoxy-1-(1-O-methyl-6-O-β-D-glucopyranosyl)-4-.alpha.-D-
 glucopyranosyl)methyl}-1,5-imino-D-glucitol.

25 The list of medicaments includes acid addition salt forms with such
 inorganic acids, such as, for example, hydrochloric, hydrobromic, sulfuric,
 phosphoric and like acids; with organic carboxylic acids such as, for example,
 acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, maleic,
 tartaric, citric, ascorbic, maleic, hydroxymaleic, dihydroxymaleic, benzoic, 2-
 30 acetoxymaleic, mandelic and like acids; and with organic sulfonic acids such as
 methanesulfonic acid and p-toluenesulfonic acid.

The sulfonylureas are a class of compounds that have been widely employed to treat diabetes. Such compounds are well known, for example as described in U.S. Pat. Nos. 3,454,635; 3,669,966; 2,968,158; 3,501,495; 3,708,486; 3,668,215; 3,654,357; and 3,097,242. Especially preferred sulfonylureas to be employed in the combinations or core formulations of this invention are glyburide, glipizide, tolbutamide, tolazamide, glisoxepid, chlorpropamide, glibornuride, gliclazide, glimepiride, phenbutamide, and tolcyclamide. Other medicaments, such as, for example, an antibiotic, a vitamin, a drug that works on the heart or in the liver, may be admixed with the active ingredients in the first layer and/or the core.

As indicated above, the modulating silicate polymer, e.g. silica gel, e.g. may be associated with the metformin core alone or with the first layer alone or with both the metformin and pioglitazone hydrochloride. The type of association as well as the concentration of the modulating agent is dependent upon the concentrations of the core active ingredient, and the layer active ingredient, the degree of coverage of the core by the first layer and the desired rate of administration of every active ingredient.

The resultant core having the first layer thereon is prepared by any conventional means known in the pharmaceutical art, e.g. compression, tableting technology, spraying technology, or encapsulation in a pharmaceutically acceptable presentation, such as a gelatin capsule. In particular, typically, the core formulation of the present invention is preferably fabricated by compression into a tablet.

The resultant core formulation of the present invention is useful to treat diabetes mellitus. Surprisingly the resultant core formulation of the invention is as user friendly and clinically effective as compared to the administration of metformin alone or pioglitazone hydrochloride alone as demonstrated by co-administration of the two agents [*Whitcomb; et al., United States Patent No. 6,011,049*], where in general, the incidence of adverse events was not influenced by age or menopausal status; and further, patients treated with the combination therapy attained better glycemic control than with either monotherapy.

It is to be understood, however, that for any particular subject being treated, e.g., a mammal, specific dosage regimens should be adjusted according to

the individual need. It is further to be understood that the dosages set forth herein are exemplary only and that they do not, to any extent limit the scope of the practice of the present invention.

The core formulation of the present invention may be administered orally, for example, with inert diluent or with an edible carrier. For the purpose of oral therapeutic administration, the core formulation may have other excipients incorporated therein. The subject core formulation may also contain the following adjuvants: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel®, corn starch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring.

The subject core formulation of the invention may contain other various materials which modify the physical form of the dosage unit (the subject core formulation), for example, as coatings. Thus, the subject core formulation of the present invention may be coated with sugar, shellac or other enteric coating agents. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

In an alternative embodiment of the present invention, the resultant core formulation (having a first layer completely or partially covering the core), is treated whereby an outer shell is formed, at least a portion of which comprises the biodegradable modulating silicate material is present in an amount having a predetermined rate of degradation or metabolism in the host being present treated.

The silicate material is a high molecular weight compound, which is physiologically acceptable and excreted from the body of the human being or other animal almost intact.

The biodegradable silicate material, comprising the outer shell, having a predetermined rate of degradation or metabolism or break down, is selected from silic acid and its derivatives, examples of which include those listed previously. Other materials well known in the art, which do not react with metformin and/or pioglitazone hydrochloride such as biodegradable polymers, like

polyorthoesters, polyanhydrides, polyamides based on glutamic acid, polyalkyl cyanoacrylates, polyesters of lactic and glycolic acid, polyactide polymers, cellulosic polymers, polyvinyl acetate, polyvinyl alcohol, polyvinylchloride, natural and synthetic rubbers, polyacrylates, polystyrene, etc. may be used. Additionally,
5 reference is made to U.S. Patents Nos. 4,166,800, and 4,389,330, which disclose additional shell forming materials and are incorporated hereinto by reference in their entirety.

The shell encapsulating the particles of pioglitazone hydrochloride of the first layer and/or the particles of metformin of the core is obtained by any
10 conventional microencapsulation process whereby microspheres of metformin and/or pioglitazone hydrochloride are formed, e.g. a solvent removal process, a phase separation technique, coacervation etc. In this regard reference is made to U.S. Patents Nos. 4,166,800 and 4,389,330, Conte et al, *J. Controlled Release*, vol. 26, (1993), pages 39-47; and U.S. Patent No. 4,839,177; all of which are
15 incorporated hereinto by reference in their entirety.

In a variation of the above alternative embodiment, the resultant core formulation is treated whereby only the top surface area of the first layer comprising pioglitazone hydrochloride has a shell coating thereon. In this regard, reference is made to U.S. Patent No. 5,916,584, incorporated hereinto by reference in its entirety,
20 which describes the process for forming such a shell. The resulting core formulation having the first layer encapsulated by the shell comprising the shell material, is one which provides a delay time prior to release of the active ingredients, i.e. pioglitazone hydrochloride and metformin, to the patient being treated for diabetes mellitus.

25 In a second alternative embodiment of the present invention, the resultant core formulation (having a first layer completely or partially covering the core) is treated whereby an outer shell comprising a natural polysaccharide, in its free acid or salt form such as guar gum; gum arabic; gum karaya; gum Benjamin, plantago ovata gum; agar; carrageenan; cellulose; gelatin; pectin; or galacturonic
30 acid is formed which encloses the particles of the first layer and/or the core.

Silicates are naturally occurring polymers consisting of silicon chains. These polymers have the propensity to absorb water thus swelling to

become gel-like structures in solution. The gel dissolves slowly thus releasing its drug payloads in a dissolution controlled manner.

The silicate shell, provides excellent stability to the core formulation while at the same time modulates drug release. Upon ingestion by a patient being
5 treated, the silicate shell swells to become a gel-like structure in solution in the body of the patient, e.g. the stomach. The gel ultimately dissolves slowly, e.g. typically, in several minutes to a few hours, usually within a day, releasing its drug payload, e.g. metformin and/or pioglitazone hydrochloride in a dissolution controlled manner.

The shell is formed using any conventional coating technique, as
10 previously discussed, see U.S. Patents Nos. 4,166,800 and 4,839,177.

The rate of release is dependent on the shell's thickness and amount of the polymeric material contained therein for a particular medicament formulation. Typically, for a release of of about 2 to 6 hours, the thickness ranges from about
0.0001 mm to about 1 mm with a concentration of the polymeric material ranging
15 from about 10 ppm to about 100,000 ppm.

In a variation of the above second alternative embodiment, the polysaccharide polymeric material, e.g. silicate, may be incorporated into or combined or mixed with the first layer comprising metformin and/or the core of pioglitazone in an effective amount to provide the desired stability and controlled
20 release of these medicaments. Typically, the silicate is provided in an amount ranging from about 10 ppm to about 100,000 ppm, in one both or of the medicaments to effect a desired release profile e.g. 15 minutes to about 12 hours of one or both of the medicaments of the core.

As discussed above, it is to be understood that the resultant core
25 formulation may be treated with the polymeric material whereby only the top surface area of the first layer comprising pioglitazone hydrochloride has a coating hereon. In this regard reference is again made to U.S. Patent No. 5,916,584. Thus as described above a delay time is provided prior to release of the release of the medicaments.

30 It is to be understood that for either metformin or pioglitazone, any pharmaceutically acceptable form thereof can be employed. Such a form encompasses the free acids, free bases, salts and various hydrate forms, including

semi-hydrate forms of these medicaments, as well as other pharmaceutical materials which are used in the formulation process as acceptable excipient materials generally known to those skilled in the art.

It is understood that any one of the biguanides, i.e. drugs having the action of the stimulation of anaerobic glycolysis, is covered by this invention as these, like metformin, increase the sensitivity to insulin in peripheral tissues of the host, e.g. a human being or another animal. These compounds also are involved in the inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of other typical biguanides included in this application are phenformin, buformin etc.

We claim:

- 1: A core formulation comprising,
 - (a) a first layer comprising pioglitazone hydrochloride or a pharmaceutically acceptable salt thereof as an active ingredient,
 - 5 (b) a core, at least a portion of which is enclosed by said first layer, comprising a biguanide as an active ingredient; and
 - (c) a modulating polymer comprising a silicate which is associated with at least one of said active ingredients.
2. The formulation of claim 1 wherein said polymer is associated
10 by forming an enclosing shell.
3. The formulation of claim 1 wherein said polymer is associated by being combined with said at least one of said active ingredients.
4. The formulation as defined in claim 1 wherein said polymer is associated by covering at least a portion of said first layer to provide a
15 predetermined delay in the time period of release of at least said pioglitazone hydrochloride.
5. The formulation as defined in claim 1, wherein said modulating polymer comprises a silicate selected from the group consisting of silicic acid, disilicic acid, trisilic acid, metasilicic acid, and orthosilicic acid in their free or
20 salt forms; silicon dioxide in either of its amorphous, crystalline, or precipitated forms; diatomaceous earth; Fuller's earth; Kieselhurh, Celite; talc; attapulgite; micas; montmorillonite, kaolin, aluminum oxide (Hydrargilite), bentonite, pumice; silanes and siloxanes and a mixture of any of the foregoing polymers.
6. The formulation as defined in claim 5, wherein said biguanide
25 is metformin.
7. The formulation as defined in claim 6, wherein said pioglitazone hydrochloride is present in an amount ranging from about 1 mg to about 45 mg; said metformin is present in an amount ranging from about 10 to about 4000 mg.
8. The formulation as defined in claim 6, wherein said
30 pioglitazone hydrochloride and/or said metformin are present as biodegradable microspheres.

9. A method of administering pioglitazone hydrochloride and metformin to a mammal, which comprises treating the mammal with the formulation defined in claim 6.

10. A method of producing a controlled release formulation,
5 which comprises:

(a) producing a hollow outer shell comprising a modulating polymer material comprising a silicate having a predetermined rate of degradation to provide a predetermined delay in the time period of release of the contents destined to be enclosed by said shell;

10 (b) inserting a core comprising metformin and having an outer layer comprising pioglitazone hydrochloride partially enclosing said core, into said hollow outer shell; and

(c) sealing said core within said hollow outer shell.

11. A method of producing a controlled release formulation,
15 which comprises:

(a) forming a core of the metformin;

(b) depositing a layer of pioglitazone hydrochloride on at least a portion of a surface of said core;

(c) combining a modulating polymer material with at least one of
20 said metformin or said pioglitazone hydrochloride.

12. A method of treating diabetes mellitus in a patient in need thereof, which comprises administering to the patient the formulation of claim 1 wherein said active ingredients are each present in an effective amount.

13. A pharmaceutical composition comprising an effective
25 amount of pioglitazone hydrochloride medicament combined with an effective amount of metformin medicament where at least one of said medicaments is combined with an effective modulating amount of a modulating polymer.

14. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 13.

30 15. A pharmaceutical composition comprising an effective amount of pioglitazone hydrochloride medicament combined with an effective

amount of phenformin medicament where at least one of said medicaments is combined with an effective modulating amount of a modulating polymer.

16. A pharmaceutical composition comprising an effective amount of pioglitazone hydrochloride medicament combined with an effective
5 amount of buformin medicament where at least one of said medicaments is combined with an effective modulating amount of a modulating polymer.

17. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 1.

18. A method of treating diabetes mellitus in a patient in need
10 thereof, which comprises, administering to the patient the composition of claim 6.

19. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 1 wherein the biguanide is phenformin.

20. A method of treating diabetes mellitus in a patient in need
15 thereof, which comprises, administering to the patient the composition of claim 1 wherein the biguanide is buformin.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/21615

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/32, 9/34, 9/36, 9/38, 9/40, 9/58, 9/60, 9/62, 9/64

US CL : 424/472, 478, 479, 480, 481, 491, 492, 493, 494, 496, 497

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/472, 478, 479, 480, 481, 491, 492, 493, 494, 496, 497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST 2.0, search terms: biguanide, metformin, phenformin, buformin, troglitazone, pioglitazone,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,166,043 A (IKEDA et al) 26 December 2000, see column 1, line 62 through column 2, line 15, column 11, lines 42-47, column 13, line 44 through column 14, line 4, claims 1 and 11-14.	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

"A"	document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"G"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

17 SEPTEMBER 2001

Date of mailing of the international search report

05 FEB 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JAMES M. SPEAR

Telephone No. (703) 308-1235